Experimental Neurology 286 (2016) 21–31

Contents lists available at ScienceDirect

Experimental Neurology

journal homepage: www.elsevier.com/locate/yexnr

Research Paper

Impairment of decision making associated with disruption of phase-locking in the anterior cingulate cortex in viscerally hypersensitive rats

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ARTICLE INFO

Article history:
Received 19 June 2016
Received in revised form 14 September 2016
Accepted 19 September 2016
Available online 21 September 2016

Keywords:
Decision-making
Phase-locking
Synaptic plasticity
Synchronization
Theta oscillation
Visceral hypersensitivity

ABSTRACT

Visceral hypersensitivity (VH) is a key factor of irritable bowel syndrome (IBS). Previous studies have identified an enhanced response of anterior cingulate cortex (ACC) to colorectal distension in VH rats, which can be observed up to 7 weeks following colonic anaphylaxis, independent of colonic inflammation. The induction of VH produces a change in the ability to induce subsequent synaptic plasticity at the ACC circuitry. In clinical practice, a positive link between IBS and cognitive impairments has been noted for years, but no animal model has been reported. Decision-making is a valuable model for monitoring higher-order cognitive functions in animals, which depends on the integrated function of several sub-regions of the ACC and amygdala. Using rat gambling task (RGT) in the present study, we observed an impairment of decision-making behavior in VH rats. Electrophysiological study showed a reduction of long-term potentiation in the basolateral amygdala (BLA)-ACC synapses in VH rats. Multiple-electrode array recordings of local field potential (LFP) in both BLA and ACC were also performed in freely behaving rats. Spike-field coherence (SFC) analysis revealed chronic visceral pain led to disruption of ACC spike timing and BLA local theta oscillation. Finally, cross-correlation analysis revealed that VH was associated with suppressed synchronization of theta oscillation between the BLA and ACC, indicating reduced neuronal communications between these two regions under the VH state. The present results demonstrate that functional disturbances in BLA-ACC neural circuitry may be relevant causes for the deficits in decision-making in chronic pain state.

1. Introduction

Hypersensitivity to visceral distention has been reported in patients with irritable bowel syndrome (IBS), a common functional gastrointestinal disorder (Mayer, 2008). In rats, visceral hypersensitivity (VH) can be modelled following the use of procedures that lead to colonic anaphylaxis (Gao et al., 2006). Based on this animal model, our group was the first to propose an involvement of ACC in VH (Gao et al., 2006). Subsequently, we have demonstrated that the perigenual anterior cingulate cortex (pACC) modulates the sensory aspect of visceral pain in VH rats (Gao et al., 2006; Wu et al., 2008). Overexpression of the NR2B receptor and T^{286}CaMKII in ACC results in increased visceral pain (Cao et al., 2008; Fan et al., 2009; Li et al., 2012). The ACC also participates in the affective component of visceral pain. Using the colorectal distension-induced conditional place avoidance paradigm, Yan et al. showed that glutamatergic activation of anterior cingulate cortex mediates visceral pain memory in rats (Yan et al., 2012). Furthermore, recent studies have shown that postprandial release of CCK-8 can activate vagal afferent C fibers, and this enhances memory consolidation and retention involved in long-term visceral negative affective states (Cao et al., 2012; Zhang et al., 2013).

Human studies have suggested that chronic pain alters normal processing in the ACC, which could account for deficits in cognitive function (Moriarty et al., 2011). The clinical connection between visceral pain and the increases in levels of anxiety, depression, as well as cognitive disorders, has long been recognized (Labus et al., 2013; Larsson et al., 2012). Symptoms of major depressive disorder (MDD) occur in up to 90% of patients with IBS (Friedrich et al., 2010). Remarkably, these emotional and cognitive signs are far less studied than the sensory components of visceral pain. Thus, the biological basis of the affective and cognitive changes in chronic visceral pain state remains poorly understood.

The responses of neocortical neurons can be persistently modified by alterations in sensory experience. Synaptic connections between

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http://dx.doi.org/10.1016/j.expneurol.2016.09.010
0014-4886/

neurons are in a near-incessant state of modification (Zhuo, 2007). At the cellular level, activity-dependent plasticity in synaptic strength, such as long-term potentiation (LTP) has been considered one of the major cellular mechanisms underlying learning and memory. It also serves as one of the key synaptic mechanisms reflecting cortical plasticity. Recently, we have showed long-lasting potentiation of local field potential in the medial thalamus (MT)–ACC synapses in VH rats (Wang et al., 2015). Theta burst stimulation in the MT reliably induced LTP in normal rats; however, induction of VH effectively blocks the expression of LTP at MT-ACC synapses. It appears that induction of visceral hypersensitivity produces a change in the ability to induce subsequent synaptic plasticity at the MT-ACC pathway. We hypothesize that the mechanisms of ACC synaptic metaplasticity are involved not only in the processes of modifying the visceral pain sensitivity, the aversive responses to pain, but also further affect the processing of learning and memory in chronic pain state. The chronic visceral pain related emotional and cognitive disorders may be associated with functional disruption in the ACC circuitry.

The ACC is a part of medial prefrontal cortex (mPFC) (Rosenbloom et al., 2012), which was defined as the cingulate cortex, area 2 (Cg2), and the prelimbic cortex with overlying cingulate cortex, area 1 (Cg1) in the present study. This definition has been well demonstrated in our previous publications (Gao et al., 2006; Wu et al., 2008; Wang et al., 2015). The induction of synaptic plasticity is favored by coordinated action-potential timing across populations of neurons rising oscillations of different frequencies (Markram et al., 1997), recorded in local field potentials (LFP). Oscillatory brain activity in the theta (4–10 Hz) frequency range, and the coherence of theta and action potential activity are believed to play an important role in many cognitive functions (Rutishauser et al., 2010). We hypothesize that disturbances of the coherence in the ACC neural firings and ongoing theta oscillatory of LFP contribute to suppress synaptic LTP. The disruptions of the theta synchronization in ACC neural circuitry are involved in mood and cognitive dysfunction in chronic visceral pain.

Decision-making is a valuable model for monitoring higher-order cognitive functions in animals (Xu et al., 2015). In the current study, we made use of the rat gambling task (RGT) and showed a decrease in the percentage of good decision-makers in the VH group. The tight functional interaction between the ACC and the basolateral amygdala (BLA) has been well demonstrated (Floresco and Ghods-Sharifi, 2007). Patients with lesioned amygdala performed worse in the Iowa Gambling Task (IGT) as well as in recognizing emotional facial expressions (Bechara et al., 2003; Damasio, 2003). A functional magnetic resonance imaging study in human (Xiao et al., 2013) found that binge drinkers who performed worse in the IGT exhibited increased activity in the left amygdala relative to their controls. Thus, it appears that higher activities in the amygdala may also be correlated with poor decision making in humans. In this study we then studied long-lasting potentiation of LFP in the BLA-ACC synapses. Multiple-electrode array recordings were performed, and indicated impaired phase relationship between ACC spikes and BLA theta oscillations in VH rats. Finally, cross-correlation analysis revealed visceral hypersensitivity led to suppressed synchronization of theta oscillations between the BLA and ACC, suggesting disturbed neuronal communication between the BLA and ACC. The data are particularly intriguing in view of the recent findings that a tight coordination of spike timing with the local theta oscillation is a key index for predicting successful memory formation in humans (Rutishauser et al., 2010).

2. Materials and methods

2.1. Animals

Adult male Sprague-Dawley rats (250–350 g) were used in these experiments. The animals were kept in their home cages and maintained on a 12:12 h light-dark cycle (lights on 7:30 a.m.) with food and water provided ad libitum. All the experimental procedures were conducted according to the guidelines laid down by the NIH in the US with the approval of the Committee on the Use and Care of Animals at City University of Hong Kong, and the authorization license for performing all the tests issue by the Department of Health of Hong Kong (No. 10-4 in DH/HA&P/8/2/5).

2.2. Viscerally hypersensitive rat model

Visceral hypersensitivity in rats was induced by colonic anaphylaxis. The detailed procedures were described in our previous publications (Cao et al., 2008; Gao et al., 2006). Before visceral hypersensitivity was induced, rats adapted to their environments at least 3 days until they were injected intraperitoneally with 10 μg egg albumin (antigen) and 10 mg aluminum hydroxide (adjuvant) in 1 ml saline. From the third day to the fifth day after antigen injection, the rats were given a colonic perfusion with antigen solution at 50 μl/min for 30 min, followed by 30 mm Hg colorectal anaphylaxis for 30 s repeated 5 times with 3-min intervals. Antigen solution was composed of 10 μg/ml egg albumin, 40 mM D-glucose, and made isotonic with NaCl. Control rats were injected intraperitoneally with 1 ml saline and colorectally perfused saline for 30 min.

2.3. Rat gambling task (RGT)

7–14 days after induction of visceral hypersensitivity, rat gambling task (RGT) was performed to evaluate the decision-making behavior of rats. Rats were habituated in the testing room and handled for 5 min daily for 3 days before testing started. Rats were moderately food deprivation during the whole RGT procedures. The time of tests began at 9:00 am and ended before 1:00 pm (early phase of the light cycle) each day.

The RGT has been developed to test the decision-making capacities in rats via a conflict between immediate and long-term gratification (food reward). Operant chambers (28 × 30 × 34 cm) were used for RGT (Imetronic, Pessac, France). During the training stage, rat gradually learned the association between the nose-poke action and the release of food pellet in the food tray. Two consecutive nose-pokes in the same aperture were necessary to trigger pellet release, to make sure rats made the choice intentionally. Each rat must obtain 100 pellets within 30 min at the end of training. Then, two 5-min sessions will be conducted. The first was set as two pellets released after a choice will be made, and the second was set as one pellet, to habituate rats for the variation of pellet number during the test. The training phase usually lasted 7 to10 days.

The 60-min test was performed the following day. Rats were allowed to freely make choices among the four apertures (A–D) as they did in the training phase, however, different choices were associated with different outcomes. The disadvantageous choice A or B related to two pellets obtained each time as immediate reward, but had a high probability of triggering a long time-out (50% probability to trigger a 222-s time out or 25% probability to trigger a 444-s time out); advantageous choice C or D associated with one pellet reward each time, but also less penalty (50% probability to trigger a 12-s time out or 25% probability to trigger a 6-s time out). Although the immediate reward of choice A and B was two times of C and D, in the long run, the theoretical maximum benefit of C and D will be five times higher than A and B. The numbers of nose-pokes of rat, food pellets released and each choice made were recorded by the POLY software. Number of nose-pokes per min during the last training session and the duration of the last training session were used to access the general activity and motivation of rats to perform the task. The proportion of advantageous choices $((C + D)/(A + B + C + D)) \times 100\%$ and food reward obtained across the test were used to identify decision-making behavior of rats.